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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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GROUP ART UNIT: 1743

S.N.: 10/051,845

EXAMINER: GAKH, YELENA G.

FILED: 01/17/2002

FOR: METHOD OF DETECTING OXIDIZING ADULTERANTS IN URINE

Commissioner of Patents and Trademarks
BOX NON FEE AMENDMENT
Washington, D.C. 20231

Madam:

In response to the Office Action dated 10/15/2003 applicant respectfully requests reconsideration of rejection of claims 1-10 based on the following amendments and remarks.

Amendments and Remarks

Responses to detailed action page 2 of office action dated 10/15/2003

1. Applicant begs your pardon as regards the proper spelling of the N,N,N',N'-tetramethyl compounds. Corrections are included. I wish, however, to point out to you that the two compounds you stated as being one and the same are in fact 2 different compounds. I refer you to Chemical Abstracts Registry and numbers {366-29-0} and {100-22-1}. These numbers refer to N,N,N',N' - tetramethyl benzidine and N,N,N',N' - tetramethyl 1,4 - phenylenediamine, respectively,

Response to the claim rejections pages 3 and 4:

1. As the courts have stated. "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention

is rendered obvious. This court has previously stated that one cannot use hind sight construction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.” (re Fritch supra, 1784). The courts further noted that “Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so.” (re Fritch, 23 USPQ 2d 1780, 1783 [CAFC 1992])

The Smith method purports to teach a method that is specific for Nitrite reductase or Nitrite quantitation. It does not claim nor does it In Fact react with a broad range of other inorganic oxidants (e.g. Sodium Hypochlorite, Chromate - Cr VI, Hydrogen Peroxide, Potassium Iodate.....etc.)

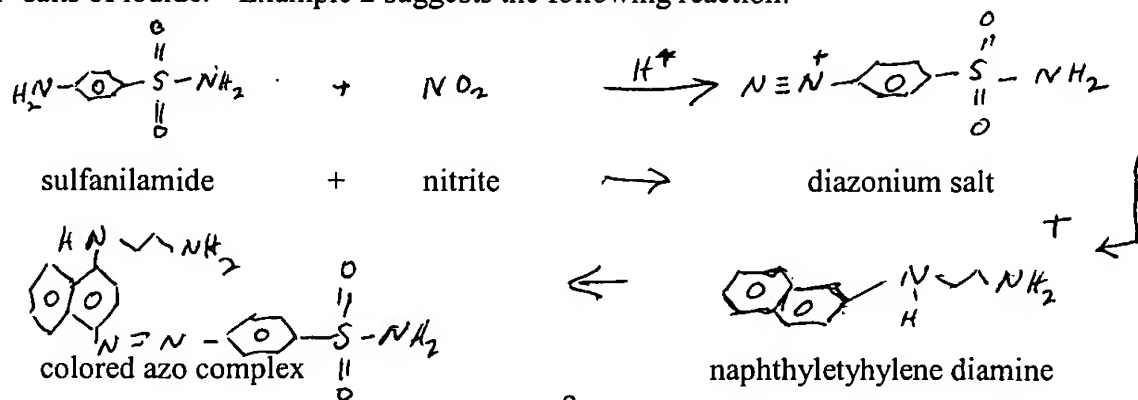
The Smith embodiment does mention the possible addition of "a salt of iodide".

It does not, however, describe its purpose or its effect in that instant invention.

Furthermore, he does not include it in ANY examples or in any claims.

The reasons for this omission are clear when the chemistry of the reactions are considered. It should consequently be clear that inclusion of the "salts of iodide" was in error and should not be an issue when considering the merits of this instant invention.

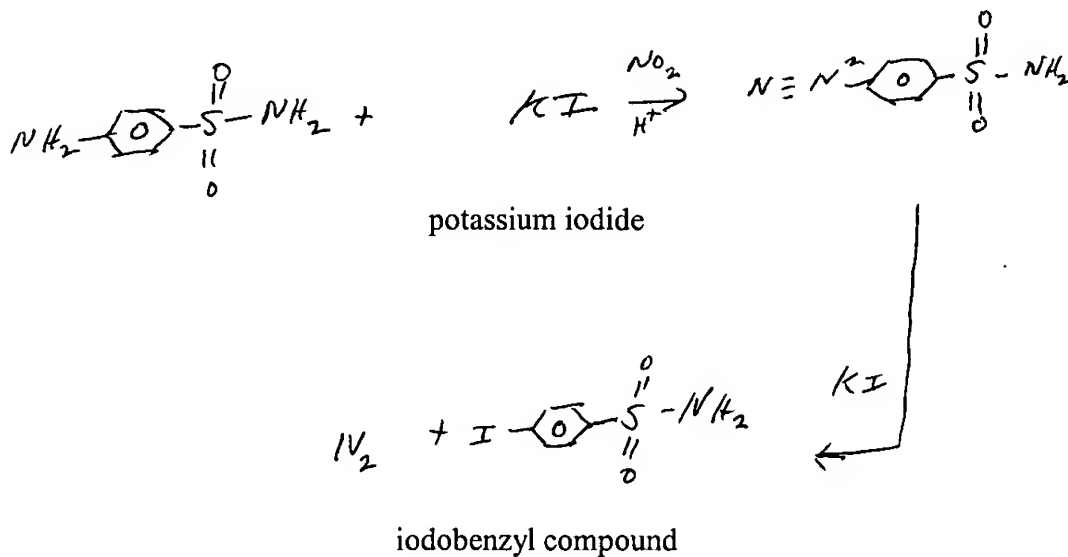
First let us consider the 6 examples as described by Smith. We can disregard examples one and four because they are enzymic assays and were specifically excluded from use in combination with "salts of iodide." Example 2 suggests the following reaction:



The diazonium compound reacts with a phenol group or an aromatic tertiary amine to form an azo dye. This mechanism serves the examples 2, 3, 5, and 6. I would note, however, that the example as described in no. 3 would "self oxidize" after a period of time making this unsuitable for any commercial product.

In addition, while example 5 is technically a tertiary amine. I believe that the ring structure would resist fracture and no diazo compound would result; if it did, however, produce a diazonium compound steric hindrance will prevent formation of an azo dye. Furthermore, if said azo dye did form it would be as a formazan dye and as such would be insoluble in water. An insoluble reaction product is incompatible with all automated chemistry analyzers as described in Smith's instant invention and as currently exist in the market place.

If, as Smith recites in his embodiment that "a salt of iodide" was included with either the R1 or R2 of the above noted reaction the following would most certainly occur:



Thus no azo dye is formed and no color reaction product results!

Obviously, the chemistry above negates the Smith teachings clearly, however, there are other issues which cast additional shadows of doubt on Smith's invention.

Salts of iodide (potassium / or sodium) must be in an alkaline solution to attain stability for more than a few days or weeks.

On the other hand, his indicators sulfanilamide, p-arsanilic acid naphthyl ethylene diamine, etc., require an acidic solution for long term aqueous stability. In addition, the reaction with nitrite to form diazonium compound and the end point azo dye must also be in an acidic media for the reaction to take place. If the reaction is basic the coupling amine forms an ammonium salt which does not couple to form a colored azo dye. The concentration of the diazonium compound is also maximized at an acidic pH.

You might suggest - although Smith does not - that one could put the iodide in R1 and make it basic and the sulfanilamide and NED in R2. Again the problem becomes one of long term stability because those two compounds in the same solution are not compatible over the long term. In addition, the iodo intermediate will compete in the reaction and depress the azo dye production.

The examiner is asked to study the Smith application in detail. This patent stresses the necessity to include compounds with "anti-oxidant activity" and "remove oxidizing contaminants". The proposed instant invention on the other hand is designed to react with all oxidants.

Including "anti-oxidants" in the Smith invention effectively blocks the oxidative effect of nitrite and therefore prevents the production of the diazonium compound. Therefore the entire premise of the Smith invention is flawed in its most basic sense.

It is also notable that dimethylaminobenzaldehyde and triphenyltetrazolium are both light sensitive making them impractical for use as reagents because of their long term instability.

Cerwonka teaches a method for making photographic images. He does not disclose any information concerning quantitative analysis of adulterating oxidants in a human sample matrix. Furthermore - he does not specifically delineate the chemistry of his color reaction - you and I can only infer it. The classic requirement for formation of an azo dye is combination of a diazonium ion with phenols or tertiary aromatic amines - not alpha carboxylic acids. In addition he presents his invention for use with emulsions on solid surfaces.

Morris, et.al., specifically describes enzymatic assays.

He describes "the interaction of cytochrome oxidase with N,N,N', N'-tetramethyl-p-phenylenediamine producing a blue color". Again, this is an enzymatic reaction. It is not the multistep diazotization reaction described in this instant invention.

In Morris's teachings the phenylenediamine compound is used as a substrate to monitor enzyme activity. In this application it is a chromophore in the determination of numerous targeted analytes (general class of oxidants).

In addition Morris notes in example #3 that the "presence or absence" of this enzyme is used in identification of both fermentative and non-fermentative bacteria. He does not speak of N,N,N', N'-tetramethyl-1,4-phenylenediamine as a "well known redox indicator", nor does he note that it "changes its color upon oxidation with oxidizers" or is used "for detecting oxidizers in urine."

The indicators as described by Cerwonka, and Morris are not what sets this instant invention apart from the prior art. It is the instant invention's ability to detect many different types of oxidants at critical levels for urine drug testing. To wit - this invention reacts with hypochlorite, chromate, nitrite, iodic acid, potassium iodate, peroxide and others. Each of these compounds has a different reaction coefficient, and produce differing colors with the chosen indicators.

The Federal Drug Testing Program as administered by SAMHSA specifies cutoffs for each adulterant , [e.g., Nitrite is 200 mg/L, Vs 20 mg/L of Chromium-CrVI].

This invention is an exact blend of reaction components and conditions to provide the appropriate sensitivity to each analyte.

For example, consider that a typical increase in absorbance units of the cutoff standard versus the zero calibrator for this assay is 1200. If a urine sample with 20 mg/L CrVI produces an absorbance equivalent to 1200 it is therefore positive.

If a urine sample with 50 mg/L of nitrite also produces an absorbance of 1200 it is a false positive because the accepted cutoff for nitrite is 200 mg/L.

A successful assay, therefore must react with considerably less intensity to nitrite versus chromium CrVI.

There is additional unique properties to this invention.

Hypochlorite is a commonly used adulterant that has been utilized by those attempting to circumvent the aims of the drug testing program for many years (see Baiker, C. J., Analytical Tox. vol 18, 1994.)

It is important to note that most drug tests do not reach the lab for testing for at least 24 hours. This lag time can easily exceed 72 hours in many cases due to regionalization of drug testing labs. While bleach in pure water is stable for months or years and readily reacts with redox indicators, this is not true for urine as a sample matrix. The hypochlorite binds to nitrogen compounds very quickly. This makes bleach “invisible” to the indicator systems as described by Smith and Morris. This instant invention, however, is still able to detect bleach in 15 ml/L levels many days after all of the free NaClO is gone.

Furthermore, the applicant has amended claims 1 and 2. The amended claims are included. The applicant believes these amendments obviate the rejections of claims 1-10 under 35 U.S.C. S112 first and second paragraphs.

In view of all of the above, it is believed that claims 1-10 are now in condition for allowance. Such action is earnestly solicited.

These amendments should negate the effect of Smith's claim to nitrite as prior art that obviates this new invention as these new claims exclude nitrite.

Again, the applicant points out that neither Smith nor Cerwonka, nor Morris teach a method to detect a number of different oxidants in urine samples submitted for Drugs of Abuse Urine testing. Morris teaches a method for making photographic images, while Morris describes enzymatic assays. In particular, Morris teaches a method utilizing an enzyme reaction with and indicator.

None of the prior art teaches a method that can detect bleach, chromate, iododic acid, iodate, and peroxide in urine samples submitted for Drugs of Abuse Urine testing. The examiner has not produced in any of the cited materials teachings that suggest combination of any of these prior art elements to form applicant's devices. For these reasons applicants are entitled to allowance of claims 1-10.

None of the references cited, but not applied, relate to detecting bleach, iodic acid, iodate, chromate and peroxides in urine samples submitted for Drugs of Abuse in Urine testing of applicant's claims 1-10. Taking all the elements from the references the examiner cites, the applicants' device is not created. The examiner uses hind-sight to suggest that one having

ordinary skill in the art would detect the aforementioned compounds in urine samples to be tested for Drugs of Abuse in Urine.

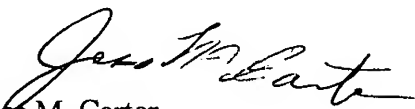
“Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so.” In re Fritch, 23 USPQ 2d 1780, 1783 (CAFC 1992)

Taking the references cited by the Examiner together one finds no suggestion to combine all of these elements to produce a device similar to the applicants. As the courts have stated, “It is impermissible to use the claimed invention as an instruction manual to ‘template’ or piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that one cannot use hindsight to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.” in re Fritch supra, 1784.

Applicant’s invention of claims 1-10 is not obvious over the prior art because such prior art as a whole does not teach applicant’s invention. Rather, some of the prior art teaches various aspects of nitrite detection, photo plate making, and enzyme assays; none of the prior art teaches the techniques of assaying for bleach, iodic acid, iodate, chromate and peroxidases in urine samples to be tested for Drugs of Abuse in Urine. The examiner has not produced, in any of the cited materials teachings that suggest combination of any of these prior art elements to form applicant’s device. For these reasons applicants are entitled to allowance of claims 1-3.

In view of all the above, it is believed that claims 1-3 are now in condition for allowance. Such action is earnestly solicited.

Respectfully submitted,


Jesse M. Carter